status of the host. It should be emphasized, however, that the results in swine were related wholly to effects of formolized virus, whereas the findings in man were related to the effects of possible actual infection with active virus followed by vaccination. Further, the group of swine studied had been treated under controlled conditions in contrast with the people who were chosen at random. For example, in the present work the animals with the highest titer before second vaccination were those revaccinated after the shortest interval between vaccination when conditions for response were not optimum; in the group of people, those with the highest titers may have represented either the best reactors or those recently recovered from the disease.

The results of the experiments with swine were similar to those of Hirst, Rickard, Whitman and Horsfall[6] in indicating rapid loss in antibody titer subsequent to vaccination, regardless of the sequence of vaccination.

Summary. The antibody response of swine to second vaccination with formalin-inactivated swine influenza virus was greatly influenced by the period between vaccinations. Second vaccination at intervals of one to four weeks resulted in antibody titers and amounts progressively greater in direct relation to the length of the interval. In parallel higher antibody levels were maintained for longer periods in those animals receiving the second vaccination after the longer intervals. Considering the height of titer after the second vaccination, together with the rapid loss of antibody after the first injection, the interval between vaccinations optimum for maintenance of the highest antibody levels appeared to be about three weeks.

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Absorption of Penicillin from the Nose and Alimentary Canal.

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To obviate the necessity for parenteral injection of penicillin other routes have been sought. Administration by mouth, including enteric capsule and duodenal tube, and by rectum have been tried as summarized previously.[1] Although satisfactory absorption results from several such combinations or procedures, the efficiency falls short of that from injection of the drug.

In this report, the relative absorption by various routes in man and animals are compared.

Absorption from the Alimentary Canal of Rats. Under sodium pentobarbital anesthesia (35 mg per kg intraperitoneally), rats were given penicillin intramuscularly and in ligated sections of the alimentary tract as follows: esophagus, stomach, duodenum (3 cm), ileum (3 cm), colon (3 cm). Ten animals were used for each route, with doses of penicillin varying from 500 to 12,500 u. per kg, body weight. Blood was taken from the heart 30 minutes later for penicillin assay. Assays were made by the method of Wolohan and Cutting[2] on whole blood. The average results, in units per cc of blood, were as follows: esophagus 0.08, stomach 0.02, duodenum 0.02, ileum 0.03, colon 0.02, intramuscular 0.11.

It is evident that absorption in the rat occurs from the stomach, duodenum, ileum, and colon about equally, but only about one

1 Cutting, W. C., Halpern, R. M., Sultan, E. H., and Armstrong, C. D., *J. A. M. A.*, 1945, **129**, 425.

2 Wolohan, M. B., and Cutting, W. C., *J. Lab. and Clin. Med.*, 1945, **30**, 161.

TABLE I.
Average Blood Concentration of Penicillin after Intramuscular, Intranasal, and Oral Administration.

	15 min	1 hr	2 hrs	4 hrs
Intramuscular	—	0.19	0.16	0.08
Intranasal	0.05	0.04	0.03	0
Oral	0.03	0.04	0.03	0.03

fifth as well as from intramuscular injection. The surprisingly high concentrations after esophageal administration are interesting, but probably of no practical value.[1]

Oral and Nasal Absorption in Dogs. Penicillin was given to 8 dogs: 2 intramuscularly, 3 intranasally (pentobarbital anesthesia, 35 mg per kg intraperitoneally), and 3 orally (esophagus ligated, same anesthesia). The dose in each instance was 1000 U. per kg, body weight, in physiological salt solution containing 100,000 U. per cc. Blood was obtained at approximately 15 minutes, and 1, 2, and 4 hours, for penicillin estimations. The average results (Table I) indicate a similar low absorption from the mouth and nose, and several fold higher blood levels after intramuscular injection.

Effect on Ciliary Activity in Frogs. The effect of penicillin on ciliary activity was studied because of the possible use of ciliated membranes (nose) as absorptive areas.

Isolated frog esophagus was split longitudinally into halves, laid flat on a cork-board, and moistened with Ringer's solution. The reciprocal of the average time (of three readings) for a small granule of cork to travel 1 cm distance was taken as the initial activity. Next a cotton pledget soaked with Ringer's solution was applied to one-half of the esophagus (control) and a pledget soaked in penicillin in Ringer's solution to the other half, each for 5 minutes. Then the ciliary activity was re-determined in the same way. The percents of ciliary activity in the penicillin-treated strips, as compared with the controls, were +110%, +53%, and +21% of the initial values for penicillin concentrations of 12,500, 25,000, 50,000 U. per cc respectively. Concentrations of 100,000 U. per cc caused complete stoppage of ciliary activity, which recovered gradually after 30 minutes. The results are presented in Fig. 1.

In general, it appears that penicillin, in low concentrations, causes a slight, though fleeting, stimulant effect on ciliary activity, while higher concentrations (more than 25,000 U. per cc) cause depression, and finally stoppage with 100,000 U. per cc. However, the depression is fairly readily reversible on standing (½ to 2 hours) with washing.

Intranasal Absorption of Penicillin in Man.

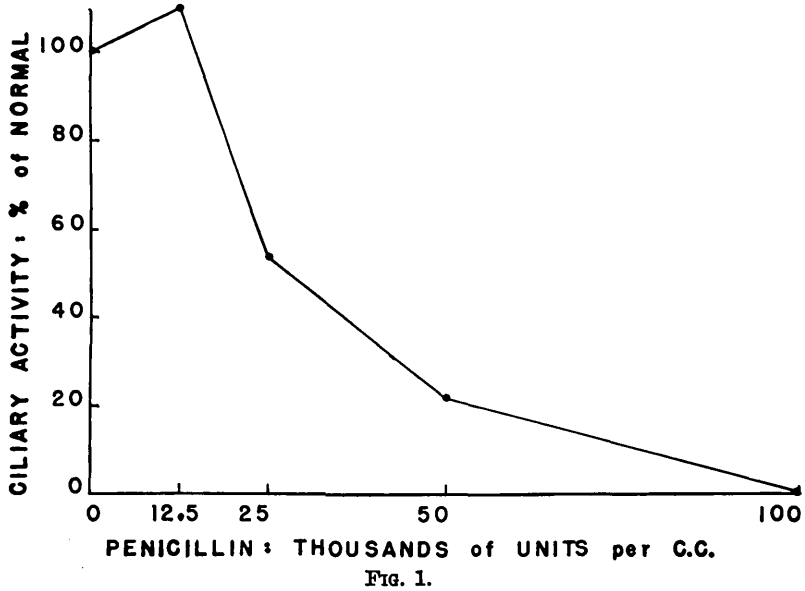

FIG. 1.
The effect of penicillin on ciliary activity in frog esophagus.

The nose was tested as a site for the absorption of penicillin in man. Preliminary trials with solutions of the agent in physiological salt solution dropped into the nose showed that concentrated solutions (100,000 U. per cc) were too irritating for general use. Intense burning, lasting for 10 seconds to a minute, was produced, and could not be circumvented by incorporating 15% saligenin or 1% tetracaine. The use of cottonseed oil, 5% dextrose, or 50% carbowax 1200 likewise did not prevent a burning sensation.

When penicillin was sprayed into the nose from a clinical hand atomizer, however, little or no irritation was experienced with solutions containing 100,000 units per cc. In several persons, repeated administrations, at 2- or 3-hour intervals, were given, without the production of disagreeable symptoms. One-fourth cc was well retained in the nose, while 0.5 cc overflowed into the posterior pharynx. The penicillin was usually placed in a short (about 3 cm) test tube, which was placed inside the bowl of the atomizer, and into which the exhausting tube dipped.

The concentration of penicillin in the blood after the administration of 25,000 units in 0.25 cc of physiological salt solution by nose was estimated at 30-minute to 1-hour intervals for 2 or 3 hours in 29 trials in 10 normal persons, and in 12 patients without upper respiratory disease.

As many bloods contain an appreciable amount of antistreptococcal activity,[3] which would enhance the activity of any penicillin present, control assays were made on initial samples of blood, before the penicillin was administered, and any indicated activity was subtracted from subsequent estimations. From the 29 trials, a total of 94 blood estimations were obtained, with an average penicillin concentration of 0.02 U. per cc. The highest concentration obtained was 0.06 U. per cc (9 trials), while in 7 trials no absorption could be demonstrated. Within the 2 to 3 hours of the test variations from 0 to 0.06 U. per cc might occur, but the average concentration at the end of the trial period (0.02 U. per cc) was the same as the average of the initial readings, showing a rather steady absorption, in contrast to that by other routes.

Since a blood concentration of 0.02 U. per cc cannot be considered adequate for treatment of most systemic infections, the intranasal route is not of promising value in this direction. However, the combination of a low blood and tissue concentration, together with a high local concentration in the nose, may be of value in the treatment of upper respiratory infections of bacterial origin. At present, trials are in progress in acute colds (following the initial and presumably virus stage) and sinusitis.

Discussion. In an attempt to avoid parenteral injection, the absorption of penicillin from a number of other sites was studied. Absorption can be demonstrated from the nose, and from practically any part of the alimentary tract, in animals. The sites of greatest promise appear to be the upper intestine and the nose. The latter organ has been inadequately tried in this connection, and although resulting systemic concentrations are low, and somewhat variable, they may not be without merit in upper respiratory tract infections, in connection with the high local concentration simultaneously produced.

Conclusions. 1. Penicillin is absorbed from the esophagus, stomach, duodenum, ileum, or colon of rats about one-fifth as well as from intramuscular injection. 2. Penicillin is also absorbed from the nose or mouth of dogs about one-fourth as well as from intramuscular injection. 3. Concentrations higher than 25,000 units of penicillin per cc depress, reversibly, the ciliary activity in frog's esophagus. 4. Penicillin may be sprayed into the nose in concentrations of 100,000 units per cc without producing significant irritation. 5. Although the blood concentrations following intranasal spraying of penicillin are low, they may enhance local antibacterial effects in the upper respiratory tract.

[3] Elias, W. F., Merrion, H. J., and Speicher, T., *Science*, 1945, **102**, 223.